201-15969

JuanB Perez/DC/USEPA/US
07/20/2005 07:53 AM

To NCIC HPV@EPA
cc
bcc
Subject Fw: Submission of Response to EPA Comments and Revised Test Plan and Robust Summaries for Anethole by the FFHPVC Terpene Consortium

----- Forwarded by JuanB Perez/DC/USEPA/US on 07/20/2005 07:53 AM -----

"Adams, Tim " <tadams@therobertsgroup.net>
07/19/2005 02:07 PM

To NCIC OPPT@EPA, Rtk Chem@EPA
cc skrixer@chemintox.com
Subject Submission of Response to EPA Comments and Revised Test Plan and Robust Summaries for Anethole by the FFHPVC Terpene Consortium

From: Adams, Tim

Dear Administrator:

On behalf of the member companies of the Flavor and Fragrance High Production Volume Consortia, the Terpene Consortium is pleased to submit a letter responding to the EPA comments on the chemical "Anethole". We also wish to submit a revised test plan and revised robust summaries for this chemical. These documents represent the final submission by the Terpene Consortium for this chemical. The cooperation of our Consortium with EPA has not only led to the accumulation of relevant hazard data on anethole but has also provided many benefits both to the industry and to the public. Our Consortium values the experience.

Respectfully,

Timothy B. Adams, Ph.D.

Technical Contact Person for FFHPVC


2005 Revised Test Plan for Anethole.pdf


2005 Final response to EPA comments-03-05.pdf


2005 Revised Robust Summaries for Anethole with Revisions.pdf

The Flavor and Fragrance High Production Volume Consortia (FFHPVC)

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May 31, 2005

Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue N.W.
Washington, D.C. 20460

Dear Administrator:

On behalf of the Flavor and Fragrance High Production Volume Consortia, I wish to thank the Environmental Protection Agency (EPA) for their comments on the test plan and robust summaries on the Chemical Category "Anethole (isomer unspecified) and *trans*-Anethole". The Terpene Consortium, as a member of FFHPVC, serves as an industry consortium to coordinate testing activities for terpenoid substances under the Chemical Right-to-Know Program. Since 1999, the twenty-one (21) companies that are current members of The Terpene Consortium have supported the collection and review of available test data, development of test plans and robust summaries for each of the sponsored chemicals, and conducted additional testing.

Based on our initial recommendations for testing and the peer-reviewed comments of the EPA, the Terpene Consortium of the Flavor and Fragrance High Production Volume Consortia (FFHPVC) is pleased to submit the following revised test plan and robust summaries for the Chemical Category, "Anethole (isomer unspecified) and *trans*-Anethole". The revised test plan and robust summaries contain additional data that addresses the questions and comments made by the EPA in its letter dated 4/4/2003. These responses taken together with the inclusion of new data and other information constitute the key changes to the original test plan and robust summaries.

Based on the total database of information for this chemical category, the Terpene Consortium concludes that the experimental and model data for physiochemical properties, environmental fate, ecotoxicity, and human health endpoints are consistent for the two members of this chemical category. The database of information on category members permits one to reliably predict endpoint values for untested members of the category. Therefore, these data support the inclusion of the two

listed substances in the chemical category and would allow for other structurally related anethole derivatives to be included in the chemical category.

In an EPA letter dated 19 October 2001 concerning HPV-sponsored chemicals that are recognized as GRAS by the Food and Drug Administration, it was pointed out that:

" It may well be, on the basis of experience gained over years of use, that most of the substances have little compelling evidence suggesting that testing is needed in the context of the HPV Challenge Program. Nonetheless, while this line of reasoning could have been used to support the recommendation not to test the substances in this category, the information was only provided as background; few examples, and no actual data, were cited."

Without prior guidance from EPA, the Terpene Consortium felt responsible to report endpoint data for these substances. Most of these data have already been provided to the US Food and Drug Administration and the World Health Organization during their evaluation of these substances as food additives. The two anethole derivatives that constitute the members of this chemical category have been reviewed by the World Health Organization/Food and Agriculture Organization Joint Expert Committee for the Evaluation of Food Additives (WHO/FAO JECFA) for use as flavoring substances in food. As part of its responsibility, JECFA maintains on ongoing program of review of the safety of food additives (WHO Technical Series Nos. 38, 40, 42, 44, 46, 48, 50). In 1998, anethole [WHO Food Additive Series: 42, 1999; see Revised Test Plan] was recognized as safe for use in food.

The substances in this category are also recognized as "Generally Recognized as Safe" (GRAS) for their intended use in food by the United States Food and Drug Administration under the Code of Federal Regulations (CFR 172.515). Under supervision of the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, specifications for the commercial use of each of these substances in food are published in the Food Chemical Codex [FFC, 1996; see Revised Test Plan].

Based on the long history of use of these substances both as naturally occurring components of food and as substances intentionally added to food, the hazard assessments performed by the US FDA and WHO/FAO JECFA, and the current regulatory status for the addition of these substances to the food supply, there is no compelling evidence that these substances should be further tested for physiochemical properties and human health endpoints in the EPA Chemical "Right to Know" Program. We do, however, maintain that data on the environmental fate and ecotoxicity are relevant to the HPV Challenge program. We consider that the test plan and robust summaries for this category are final and have no plans to provide additional data. The EPA comprehensive comments provided the necessary guidance to complete the test plan for this category. A table containing the key hazard data for the two anethole derivatives has been included in this letter and in the revised robust summaries. Also included in this letter are our specific responses to EPA comments.

The collaboration between the Terpene Consortium and the Environmental Protection Agency in the Chemical "Right to Know" Program has produced a hazard database that will be useful to the public for decades to come. Thank you for the opportunity to participate in such a program.

If you have any questions or comments concerning the contents of this letter, please feel free to contact me at any time (202-331-2325) or tadams@therobertsgroup.net.

Best regards,

Timothy B. Adams, Ph.D.

Technical Contact Person for FFHPVC

Summary of Key Hazard Data for *trans-Anethole and Anethole*

Endpoint	Substance/Surrogate[1]	Value/Range[2]	Reference
Partition Coefficient	Anethole	3.39	Hansch C. *et al.*, 1995
Biodegradation[3]	Anethole	28d/91.0% (OECD 301B)	Quest International, Inc. (1994)
Fish	*trans*-Anethole	96-hr/LC50=7.690 mg/L	Broderius et al., 1990
Aquatic Invertebrates	*trans*-Anethole	48-hour LC50 = 6.82 mg/L (CL: 6.30-7.39); 48-hour EC50 = 4.25 mg/L (CL: 3.89-4.65)	Broderius et al., 1990
Aquatic Plants	*trans*-Anethole	96-hour IC50 = 9.571 mg/L (CI:7.434-13.274)	Broderius et al., 1990
Repeat Dose[4] **(route)**	*trans*-Anethole	12 month NOEL=0.46%	Miller et al., 1983
Repeat Dose (route)	*trans*-Anethole	28 d LOEL=Not determined 28 d NOEL=240 mg/kg (oral-diet)	Minnema, 1997a
Repeat Dose (route)	*trans*-Anethole	90 d LOEL=1200 mg/kg' 90 d NOEL=600 mg/kg (oral-diet)	Minnema, 1997c
Repeat Dose	*trans*-Anethole	177 wk LOEL= 0.5%	Truhaut et al.,

[1] Surrogate is a structurally related substance include a metabolic product or precursor of the named substance
[2] Experimental value or values for a substance or group of substances in the chemical category
[3] not biodegradable, (-); readily biodegradable, (+); ready and ultimately biodegradable, (++)
[4] Value is the NOEL, no observable effect level, or LOEL, lowest observable effect level (route, duration)

(route)		177 wk NOEL=0.25% (oral-diet)	1989
Reproductive (route)	*trans*-Anethole	70 d NOEL=1% (oral-diet)	Le Bourhis, 1973b
Developmental (route)	*trans*-Anethole	32 d LOEL=350 mg/kg, 32 d NOEL=175 mg/kg (gavage)	Argus Research Laboratories, Inc. (1992)
***in vitro* Genotoxicity**[5]	*trans*-Anethole	-, +/- (AMS); -, + (MLA); -, (ABS); -, +/-, UDS; [6]	Sekizawa J. and Shibamoto, T. (1982); Hsia et al., 1979; Heck et al., 1989; Nestmann et al., 1980; Swanson et al., 1979; Mortelmans, 1986; To et al., 1982; Gorelick et al., 1995; Caldwell et al., 1992; Howes et al., 1990; Marshall et al., 1996; Marshall et al., 1989; Mueller et al., 1994
***in vivo* Genotoxicity**[7]	*trans*-Anethole	-(MN); - (UDS)	Al-Harbi et al., 1995; Marshall and Caldwell, 1996

[5] (-), no significant evidence; (+/-), equivocal evidence; (+), positive evidence of genotoxicity
[6] AMS, Ames assay; MLA, Mouse Lymphoma assay; ABS, chromosomal aberration assay; UDS, Unscheduled DNA Synthesis; MN, Micronucleus test, SCE, Sister Chromatid Exchange assay, SLA, Sex-linked Lethal assay.
[7] (-), no significant evidence; (+/-), equivocal evidence; (+), positive evidence of genotoxicity

EPA Comments on Chemical RTK HPV Challenge Submission:

Anethole (isomer unspecified) and *trans*-Anethole

SUMMARY OF EPA COMMENTS

The sponsor, the Terpene Consortium of the Flavor and Fragrances High Production Chemical Consortia, submitted a test plan and robust summaries to EPA for anethole (isomer unspecified) and *trans*-anethole (CAS Nos. 104-46-1 and 4180-23-8, respectively) dated November 12, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 4, 2002.

1. Physicochemical Properties. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

2. Environmental Fate. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. Additional information is needed in the robust summaries.

3. Health Effects. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

4. Ecological Effects. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. Additional information is needed in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE ANETHOLE (ISOMER UNSPECIFIED) AND *trans*-ANETHOLE CHALLENGE SUBMISSION

General

The test plan covers two substances: *trans*-anethole, and anethole (isomer unspecified) which contains predominantly the *trans* isomer (greater than 85% when produced industrially). Because of the close structural relationship between the isomers and the similar toxic responses observed in a number of tests, only small differences in toxicity are expected for these isomers.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Stability in water. While the test plan correctly states that anethole does not hydrolyze, the submitter needs to provide this reasoning in the robust summary.

Transport and distribution (fugacity). The data provided by the submitter are adequate for the purposes of the HPV Challenge Program; however, the submitter needs to include in the robust summary the input values to the model.

Additional information has been provided in the robust summaries.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

All SIDS-level endpoints for anethole and *trans*-anethole have been adequately addressed for the purposes of the HPV Challenge Program. Although there are problems with certain aspects of individual studies and missing details, the data are acceptable on a weight-of-evidence basis for acute toxicity, repeated-dose toxicity, genetic toxicity and reproductive/developmental toxicity.

Additional information has been provided in the robust summaries.

Ecological Effects (fish, invertebrates, and algae).

The data referenced by the submitter are adequate; however, the submitter did not include critical information in the robust summaries. Although EPA has made a determination by examining the studies, the submitter needs to incorporate the missing details.

Additional information has been provided in the robust summaries.

Specific Comments on the Robust Summaries

General

The purity of the test substance was not included in many of the robust summaries.

Health Effects

Acute Toxicity. Of seventeen studies submitted, omissions included: the identification of the vehicle used, the administered doses, mortality results by dose, information on clinical signs and symptoms other than death and the method for calculating the LD_{50}.

Additional information has been provided in the robust summaries.

Repeated-Dose Toxicity. The summary of 117-week assay in rats on *trans*-anethole omitted the specific hematological parameters assessed, the organs examined for histopathology, and the mortality results by dose and sex. In addition, details concerning clinical chemistry were not reported.

Truhaut report contained no clinical chemistry data. Data on haematological parameters and organ histopathology data were added to the robust summaries

Genetic Toxicity. There are a number of omissions such as the criteria for scoring the results, the number of replicates, and the cytotoxic concentrations for the Ames assays. For a bone marrow micronucleus test, omissions included the group sizes and the number of cells examined per dose.

This information was added to the robust summaries

Reproductive Toxicity. A robust summary for a pre-guideline 4-generation reproductive toxicity test in rats exposed to *trans*-anethole in the diet did not specify the numbers of males and females that were caged together during mating or the group sizes (numbers of pregnant females) for each generation. The reported methods were consistent with OECD Guideline 416 (2-generation study) except that a single dose was administered.

During mating, each cage contained a single pair of male and female rats. These data have been clarified in the robust summary.

Developmental Toxicity. The robust summary identifies the test substance as anethole (isomer unspecified), while a published reference on p 807 identifies the test material as *trans*-anethole (Newberne, et al.). The submitter needs to resolve the discrepancy.

Substance was trans-anethole; robust summary corrected.

Ecological Effects

Fish. The submitter needs to include information on the electronic diluter used to minimize evaporation losses, flow rate, the number and volume of additions per day, the treatment concentrations used and the number of replicate tests.

The ecotoxicity test in fish was conducted with a modified Benoit diluter (Benoit, 1981) which utilized six one-liter tanks; one control and five treatments with a dilution ratio of 0.65 between each treatment. The flow to each tank was 10 ml/min giving 14.4 volume additions per day. One control and five dilutions at 100, 80, 60, 40 and 20 percent of the stock concentration comprised the exposure series. The test solution depth was measured at 4-5 cm. No replicates were used. Tanks were placed in a random sequence in a constant temperature water bath.

Invertebrates. The submitter needs to include information on the electronic diluter used to minimize evaporation losses, flow rate, the number and volume of additions per day, the treatment concentrations used and the number of replicate tests.

The daphnia test was conducted with a modified Benoit diluter (Benoit, 1981) which utilized six one-liter tanks; one control and five treatments with a dilution ratio of 0.65 between each treatment. The flow to each tank was 10 ml/min giving 14.4 volume additions per day. One control and five dilutions at 100, 80, 60, 40 and 20 percent of the stock concentration comprised the exposure series. The test solution depth was measured at 4-5 cm. No replicates were used. Stainless steal screen enclosures (forty mesh) were placed in each chamber for the daphnia exposures. Tanks were placed in a random sequence in a constant temperature water bath.

Algae. The submitter needs to include pH, water temperature, water hardness, chemical purity, and information on the type and frequency of analytic measurements used to determine the concentration of the test chemical.

Total hardness and alkalinity were measured in mg/l as CaCO3 in the high milled and low exposure tanks as well.

Reference

Newberne, et al.,1999. The FEMA GRAS Assessment of trans-Anethole Used as a Flavouring Substance, Food and Chemical Toxicology 37:789-811.